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MEMORANDUM:

SUBJECT: **Acephate**: Hazard Identification Committee Report.

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FROM: George Z. Ghali, PhD.
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Thru: Clark Swentzel
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To: Tina Levine, PM 04
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The Health Effects Division-Hazard Identification Committee met on October 30 and December 11, 1997 to evaluate the existing and/or recently submitted toxicology data in support of acephate re-registration, identify toxicological endpoints and dose levels of concern appropriate for use in risk assessments for different exposure routes and duration, and assess/reassess the reference dose for this chemical.

Material available for review consisted of data evaluation records (DERs) for a chronic toxicity/carcinogenicity study in rats (**83-5**), one-year feeding study in dogs (**83-1b**), a carcinogenicity study in mice (**83-2b**), a reproductive toxicity study in rats (**83-4**), developmental toxicity studies in rats and rabbits (**83-3a and -3b**), an acute dermal toxicity study in rats (**81-2**), a subchronic inhalation toxicity study in rats (**82-4**), a subchronic feeding study in rats, a cholinesterase inhibition

study (37-73 days) in human, a dermal absorption study in rats (85-2), acute and a subchronic neurotoxicity studies in rats (81-8 and 82-7) and a battery of mutagenicity studies (84-2).

Hazard Identification Committee members present were Karl Baetcke (Senior Science Advisor, HED), William Burnam (Chief, SAB, HED), George Ghali (Executive Secretary), Karen Hamernik, Nancy McCarroll, Susan Makris, Michael Metzger (Co-Chair), Melba Morrow (Alt. Chair), Kathleen Raffaele, John Redden, Jess Rowland, and Clark Swentzel (Chief TB II, Chairman).

In attendance also were Stephen Dapson, Sanjivani Diwan, William Sette and Felecia Fort, HED, as observers.

Hazard Identification Committee member(s) in absentia: David Anderson.

Scientific reviewer(s) (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report and concurrence with the hazard identification assessment review unless otherwise stated.

Krystyna Locke

HAZARD IDENTIFICATION

Based on comprehensive evaluation of the toxicology data available on acephate, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories indicated below:

I) DIETARY HAZARD resulting from ingestion of residues of this particular pesticide when used on agricultural food commodities for pest control or as a food additive and may include **acute and/or chronic exposure**,

II) OCCUPATIONAL/RESIDENTIAL HAZARD resulting from **dermal and/or inhalation** exposure to the chemical and may include **short-, intermediate- and/or long-term exposure**.

Issues related to the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), are also addressed.

Where no appropriate data have been identified for a particular duration or exposure scenario, or if a risk assessment is not warranted, this is noted. Levels of uncertainties associated with intraspecies variability, interspecies extrapolation, route to route conversion, or variable duration extrapolation are also addressed.

Based on the use pattern/exposure profile, the Committee determined that the risk assessments indicated below are required for acephate or as otherwise stated.

I. Dietary Exposure

A. Acute Dietary Exposure:

Critical Study: Range-finding acute study of Orthane technical in rats, (Guideline 81-8), MRID No. 44203302, HED Doc. No. 000000.

In this study, acephate (99.0% purity) was administered to both sexes of Sprague-Dawley rats as a single gavage at dose levels of 5, 25, 125 or 500 mg/kg and then to groups of females only at dose levels of 0.5, 2.5, or 5 mg/kg.

Cholinesterase activity determined at termination of the study (2.5 hours after dosing), were inhibited in a dose-related manner, in males and females, as follows: 1) in plasma, at dose

levels of 2.5 mg/kg (F) and 5.0 mg/kg (M), and above; 2) in RBC, at dose levels of 5.0 mg/kg and above; and 3) in brain, at dose level of 2.5 mg/kg and above.

Endpoint and Dose Level Selected for Risk Assessment: Plasma and brain cholinesterase inhibition in female rats with a NOEL of 0.5 mg/kg/day and an LOEL of 2.5 mg/kg.

Uncertainty Factor (UF): An uncertainty factor of 100 was recommended to account for both interspecies extrapolation and intraspecies variability.

Comments and Rational: In this range-finding study cholinesterase inhibition was observed after a single oral dose. Therefore, the selection of this study for the purpose of acute dietary risk assessment is justified.

B. Chronic Dietary Exposure-Reference Dose (RfD):

Reference Dose (RfD): 0.0012 mg/kg/day

Critical Study: 90-Day Feeding Study with Acephate: Special Cholinesterase study, (Non-Guideline Study), MRID No. 40504819, HED Doc. No. 006680.

In this study, Sprague-Dawley rats received Acephate Technical (purity: 98.2%) in the diet for 13 weeks at the nominal doses of 0, 2, 5, 10 and 150 ppm. The actual intake of the test material was 0, 0.12, 0.21, 0.58 and 8.90 mg/kg/day, respectively, for males and 0, 0.15, 0.36, 0.76 and 11.48 mg/kg/day, respectively, for females.

Brain cholinesterase was slightly inhibited in male and female rats at 2 ppm (0.12 mg/kg/day in males and 0.15 mg/kg/day in females), the lowest dose level tested. However, the response was not dose-dependent. Therefore, the Committee considered the 2 ppm to be a NOEL for brain cholinesterase. The NOEL/LOEL for erythrocyte cholinesterase inhibition were 10 ppm (0.58 mg/kg/day in males and 0.76 mg/kg/day in females) and 150 ppm (8.90 mg/kg/day in males and 11.48 mg/kg/day in females), respectively. The NOEL/LOEL for plasma cholinesterase inhibition were 10 ppm and 150 ppm, respectively, for both males and females.

Endpoint and Dose Level Selected for Risk Assessment: A NOEL for brain cholinesterase inhibition is 2 ppm (0.12 mg/kg/day in males and 0.15 mg/kg/day in females).

Uncertainty Factor (UF): An uncertainty factor of 100 was

recommended to account for both interspecies extrapolation and intraspecies variability.

Comments and Rational (if any): Minimal brain cholinesterase inhibition was observed in both sexes at 2 ppm (0.12 mg/kg/day in males and 0.15 mg/kg/day in females), the lowest dose level tested. The Committee considered the options of defining an exact NOEL through a regression analysis or applying an additional UF of 3. Instead, the Committee decided to consider the 2 ppm a NOEL for brain cholinesterase inhibition since the inhibition at this level was not much higher at the next higher dose level of 0.21 mg/kg/day, i.e. was not dose dependent. Other factors considered by the Committee in deciding on 2 ppm as the NOEL for brain cholinesterase inhibition are provided below:

Data interpretation was complicated by the fact that two different instruments were used to measure cholinesterase activities. Brain cholinesterase activities were measured at 4 weeks with a Varian DMS 100 spectrophotometer and determinations at 9 and 13 weeks were made using a COBAS/FARA centrifugal analyzer. Since the use of two instruments could possibly affect any comparison of data that could be made between weeks or over time, the discussion here will be limited to intraweek data comparison.

The levels of brain cholinesterase specific activity at 2 ppm were not always statistically significantly decreased relative to the appropriate concurrent controls or, if they were, generally displayed a shallow dose response relationship with decreases at the next higher dose level. In addition, the overlap of the relatively low levels of inhibition of brain cholinesterase specific activity at 2 ppm (about 1-7% for males and 2-9% for females) and the low coefficients of variation (< 10%) calculated for each group mean and standard deviation in the assay suggested that the cholinesterase activity values at 2 ppm were approaching or were in the range of normal biological variation and the limits of sensitivity of the assay in the performing lab.

The levels of inhibition of brain cholinesterase specific activity at 5 ppm were consistently greater (albeit only slightly) than those at 2 ppm and were consistently statistically significantly different from controls at all measurement time points for both sexes. Therefore, 5 ppm was considered to be a LOEL in the study.

II. Occupational/Residential Exposure

A. Dermal Exposure:

A dermal absorption factor is not required since a dermal NOEL from a 21-day dermal toxicity study was selected for short-, intermediate-, and long-term dermal exposure risk assessments.

1. Short Term Dermal Exposure (1-7 days):

Critical Study: 21-Day Dermal Toxicity Study in rats (82-2), MRID No. 000000. Sponsor: Valent USA Corporation, Study No VP 11879, Huntingdon Research Study No. 97-2547.

The Registrant sent a "Draft" copy of the report of a 21-day dermal toxicity study in rats with Technical Acephate. This study has NOT BEEN submitted to the Agency. However, adequate "information", that could be used for Toxicology Endpoint Selection, was provided in the "draft". Presented below is the summary of the study (*provided by Jess Rowland, Senior Branch Scientist, SAB, HED*).

Groups of Sprague-Dawley rats (10/sex/dose) received 15 repeated dermal applications of Acephate (Technical) at 0, 12, 60 or 300 mg/kg/day, 5 days/week over a three week period. Plasma, erythrocyte and brain cholinesterase activity was measured at termination. Treatment had no effect on survival, body weight, body weight gain, food consumption, hematology or clinical chemistry parameters. In females, brain cholinesterase activity was significantly ($p < 0.01$) decreased at 60 mg/kg/day (17.137 IU/g; 6%) and at 300 mg/kg/day (15.787 IU/g; 14%) when compared to controls (18.317 IU/g). In males brain cholinesterase activity was decreased only at 300 mg/kg/day (16.628 IU/g, 9%) when compared to controls (18.270 IU/g). Erythrocyte cholinesterase activity was non-significantly decreased at 300 mg/kg/day in males (1.185 IU/g, 9%) and females (1.137 IU/g, 13%) when compared to control males (1.308 IU/g) and females 1.303 IU/g). For cholinesterase inhibition, the NOEL was 12 mg/kg/day and the LOEL was 60 mg/kg/day based on inhibition of brain cholinesterase activity.

Endpoint and Dose Level Selected for Risk Assessment: NOEL of 12 mg/kg/day, based on brain cholinesterase inhibition observed at the next higher dose level of 60 mg/kg/day.

Uncertainty Factor (UF): An uncertainty factor of 100 was recommended to account for both interspecies extrapolation and intraspecies variability.

Comments and Rational (if any): Although there was an acute dermal toxicity study which may appear to be more appropriate for

use for short-term dermal risk assessment, the study was not used since the dosing regimen in this study does not cover the exposure period of 1-7 days, and repeated exposure was not evaluated in this study.

2. Intermediate-Term Dermal Exposure:

Critical Study: 21-Day Dermal Toxicity Study with Technical Acephate in rats (82-2), MRID No. 000000. Sponsor Valent USA Corporation, Study No VP 11879, Huntingdon Research Study No. 97-2547.

For the executive summary of the study and/or more information, see Section II, A-1, above.

Endpoint and Dose Level Selected for Risk Assessment: NOEL of 12 mg/kg/day, based on brain cholinesterase inhibition observed at the next higher dose level of 60 mg/kg/day.

Uncertainty Factor (UF): An uncertainty factor of 100 was recommended to account for both interspecies extrapolation and intraspecies variability.

Comments and Rational (if any): The selection of this 21-day dermal toxicity study was considered appropriate with respect to the route and duration of exposure.

3. Long-Term Dermal Exposure:

Critical Study: 21-Day Dermal Toxicity Study with Technical Acephate in rats (82-2), MRID No. 000000. Sponsor Valent USA Corporation, Study No VP 11879, Huntingdon Research Study No. 97-2547.

For the executive summary of the study and/or more information, see Section II, A-1, above.

Endpoint and Dose Level Selected for Risk Assessment: NOEL of 12 mg/kg/day, based on brain cholinesterase inhibition observed at the next higher dose level of 60 mg/kg/day.

Comments and Rational: This subchronic study was used for risk assessment for long-term duration since cholinesterase inhibition was not progressive with time.

Uncertainty Factor (UF): An uncertainty factor of 100 was recommended to account for both interspecies extrapolation and intraspecies variability.

B. Inhalation Exposure:

Critical Study: 4-Week Inhalation Toxicity Study in Rats with Acephate Technical (82-4), MRID No. 40645903.

Acephate (purity >99%) was administered by inhalation (whole body exposure) at 0 (house air only), 0.187, and 0.507 mg/cubic meter (MMAD 2.84-3.59, and 2.43-3.14; GSD 1.60-1.80 and 1.61-1.83, respectively) to Fischer 344 [CDF(F-344)/Cr1BR] rats (10/sex/group). The main exposure period consisted of 21 six-hour exposures over a 30-day period (10 animals/sex/group). All animals were rinsed in tepid tap water after exposure, to reduce topical exposure to Acephate. Five animals/sex from control and low dose groups received 12 exposures over a 16-day period, at which time they were sacrificed for determination of plasma, erythrocyte, and brain cholinesterase. In addition, 10 animals/sex from control and high dose groups were retained for 4 additional weeks after cessation of exposure (recovery group).

There was a slight, dose-related, increase in urine staining of the fur in treated females when compared to controls (maximum incidence was 2 animals in each of groups 2 and 3 during week 4). In addition, two females in Group 3 demonstrated dyspnea during study week 2. The toxicological significance of these findings is questionable. There were no treatment-related changes in body weight, food consumption, clinical chemistry or hematology parameters, plasma, erythrocyte or brain cholinesterase activity, or histopathology findings.

Based on the results of this study (lack of treatment-related effects), the systemic LOEL was considered to be >0.507 mg/cubic meter; the systemic NOEL was established at 0.507 mg/cubic meter. The LOEL for cholinesterase inhibition (plasma, erythrocyte, and brain) was established at >0.507 mg/cubic meter, with a NOEL of 0.507 mg/cubic meter.

Endpoint and Dose Level Selected for Risk Assessment: The NOEL is >0.507 mg/cubic meter (0.0005 mg/L).

Uncertainty Factor (UF): An uncertainty factor of 100 was recommended to account for both interspecies extrapolation and intraspecies variability.

Comments and Rational (if any): This subchronic study was used for risk assessment for different exposure duration provided that a margin of exposure is calculated for short- intermediate- and long-term exposure.

C. Aggregate Risk:

Because of similarity of the endpoints, the Committee recommended that separate Margin of Exposure (MOEs) be calculated for dermal and inhalation exposure. The Aggregate risk can therefore be expressed using the following equation:

$$\text{Aggregate Risk} = \text{inverse of } \frac{1}{\text{MOE}_{\text{dermal}}} + \frac{1}{\text{MOE}_{\text{inhalation}}} + \frac{1}{\text{MOE}_{\text{dietary}}}$$

III. FQPA Considerations:

Under the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency was directed to "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Pursuant to the language and intent of the FQPA directive regarding infants and children, the applicable toxicity database for acephate was evaluated by the Hazard Identification Committee, the Committee concluded the following:

Adequacy of data: The toxicology data base included an acceptable two-generation reproduction study in rats and prenatal developmental toxicity studies in rats and rabbits, meeting the basic data requirements, as defined for a food-use chemical by 40 CFR Part 158. In addition, a somatic cell assay provided information on effects in mice following prenatal exposure to acephate. There are no data gaps for the assessment of the effects of acephate following *in utero* and/or early postnatal exposure.

Susceptibility issues: There was no indication of increased sensitivity of the offspring of rats, mice, or rabbits to pre-

and or postnatal exposure to acephate. In all studies examined, maternal or parental NOELs were less than or equivalent to offspring NOELs.

Uncertainty factor: The Committee determined that for acephate the 10-fold uncertainty factor for the protection of infants and children would be removed. This conclusion was based upon the following:

1) There are no data gaps for the assessment of the effects of acephate on young animals in the standard required studies. In addition, based upon the available data, the Committee determined that a developmental neurotoxicity in rats was not required with acephate,

2) The available data demonstrated no indication of additional sensitivity to rats, mice, or rabbits following pre- and/or postnatal exposure.

IV. Carcinogenicity:

This chemical has been classified by the Health Effects Division-Carcinogenicity Peer Review Committee (CPRC). The HED-CPRC recommended that acephate be classified as a "Group C", possible human carcinogen. This classification was also supported by the FIFRA-Scientific Advisory Panel (SAP) based on statistically significant increase in hepatocellular carcinomas in mice. This classification is based on two adequate carcinogenicity studies in two animal species.

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